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Research paper

Thermochemical analysis of the dissolution process of Griseofulvin

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Abstract

Very often poor water solubility limits the therapeutic use of drug molecules. In order to develop strategies to overcome this handicap a basic understanding of this phenomenon is needed. In this paper Griseofulvin is used as a model substance. According to the Hess theorem the direct dissolution of Griseofulvin is replaced by a series of alternative processes which in their combination have the same starting point as well as the same endpoint as the direct dissolution. The energies associated with these alternative processes however can be determined more exactly than the dissolution energy. In cases where the measurement of an energy is impossible, e.g. the transfer energy of single molecules from the vapor phase into water, this energy is calculated by quantum chemical methods. In addition these alternative processes allow for a better understanding of the elementary steps involved in the dissolution process. The energies determined for the various alternative processes are compared with the dissolution energies as calculated by means of AMSOL. An excellent agreement can be observed.

Keywords: Griseofulvin; Energy; Thermochemical analysis; AMSOL; Solvation; Sublimation; Dissolution; Hess theorem

1. Introduction

Water solubility is often limiting the absorption of drug molecules from the intestine. Many attempts were made to overcome this difficulty however a real breakthrough in the solubility improvement of sparingly soluble drugs has not yet been achieved.

There are many equations allowing for the calculation of the solubility of chemical compounds under various conditions, e.g. the solubility in ideal solutions, the solubility in regular solutions. Despite good agreement between solubilities calculated according to one of these approaches and the values obtained experimentally, these equations do not help in the development of methods ensuring a high bioavailability of poorly soluble drugs.

Long before recognizing the properties of state functions Hess [4] showed that a direct way connecting two defined states A and B of a thermochemical system can be replaced by a consecutive sequence of alternative ways starting in A and ending in B. The Hess theorem shall be applied to the dissolution process in order to find explanations for the poor solubility of a given substance. This understanding should then allow for the search of methods to improve the solubility of a given drug substance. As a model compound we selected Griseofulvin.

According to Hildebrand et al. [1] the regular solubility of a compound can be described by

$$\ln X_2 = -\frac{\Delta H_\mathrm{f}}{R}\left(\frac{1}{T}-\frac{1}{T_\mathrm{f}}\right)-\frac{V_2\Phi_1^2}{RT}(\delta_1-\delta_2)^2 \qquad (1)$$

where X_2 is the solubility of the solute (subscript '2') in the solvent (subscript '1') at the temperature T. ΔH_f is the melting enthalpy of the solute at its melting temperature T_f. δ_1, δ_2 are the solubility parameters of the solvent and the solute, respectively. Φ_1 is the volume fraction of the solvent in

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solution at solubility and V_2 is the molar volume of the solute.

According to Eq. (1) the solubility of a compound can be described as the sum of two terms: its solubility in an ideal solution and the interaction between solute and solvent in a regular solution. Schematically this interaction can be visualized by Fig. 1 [2,3].

In the first step a molecule of the solid to be dissolved separates from the solid. Formally it corresponds to a sublimated molecule. In the second step a solvent molecule leaves its position thus creating a free volume which then, Step 3, can be occupied by a "sublimated" solute molecule. Eventually the solvent molecules rearrange to solvate the solute molecule.

Applying the Hess theorem [4] the dissolution process can be depicted as follows, Fig. 2.

As can be seen from Fig. 2 the dissolution energy is given by the sum of the sublimation energy, the transfer energy of the sublimated molecules into free volumes formed in the solvent and eventually the solvation energy. With poorly soluble drugs the dissolution energy is rather low. Therefore, its accurate determination may be very difficult. The energies of the alternative routes however are significantly higher. In consequence they can be determined exactly or can be calculated by quantum chemical methods, e.g. the energies of transfer and solvation. In addition a comparison of the various contributions to the dissolution energy allows one to conceive methods to improve the solubility of a given compound.

In most cases studied to date the energy of the endothermic sublimation process is almost as high as the energy of the exothermic solvation thus limiting the solubility of the compound. If during the manufacturing of a dosage form it would be possible to form a solid solution as a means to fix the energy-rich state of isolated molecules it should be possible to significantly increase the solubility of the drug.

2. Materials and methods

2.1. Griseofulvin

Griseofulvin, Fig. 3, was used as supplied by the Arzneimittelwerke Dresden, AWD (Dresden Germany). The particle size was smaller than 5 µm. The tests for identity, purity and content were performed by the supplier.

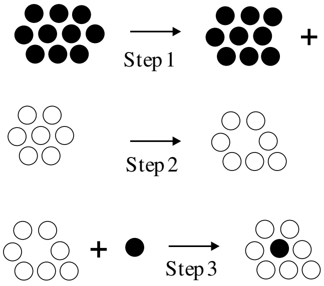

Fig. 1. Interaction between solute and solvent (isomegetic solutions).

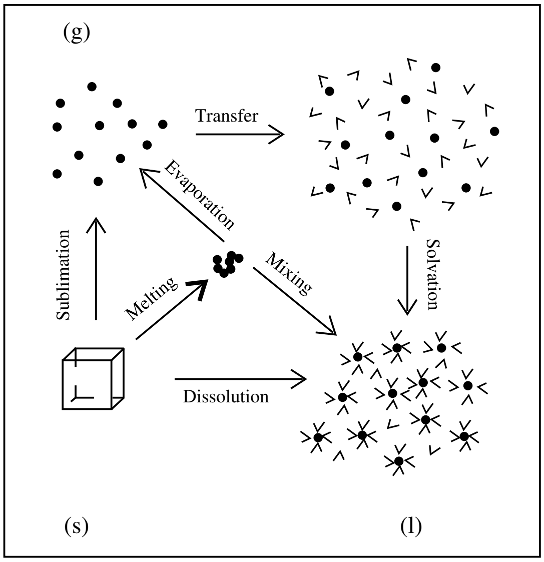

Fig. 2. Alternative ways to describe the dissolution process according to Hess.

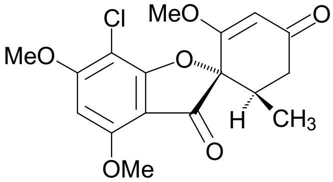

Fig. 3. Structure of Griseofulvin, molecular weight = 352.77.

2.2. Distilled water

The water used in the experiments was prepared as follows: freshly distilled water was filtered (Filter: Schleicher and Schüll FP 030/3, 0.2 µm, Dassel, Germany) into bottles of 100 ml and then autoclaved at 121 °C, 2 bar, 15 min. Until its use it was stored at 8 °C. At 20 °C the pH of the water was in the range of 6.8–7.0 (pH-meter 620, Metrohm, Herisau, Switzerland).

2.3. Determination of the Griseofulvin concentrations in water

The concentration of Griseofulvin dissolved in water was determined by UV-spectrometry (Perkin-Elmer UV/vis spectrometer Lambda 14, Überlingen, Germany) using quartz cells (Hellma Quartz Suprasil, Mülheim, Germany), optical path $d = 1$ cm. The UV absorption spectrum for Griseofulvin is shown in Fig. 4 to have a lambda max at 295 nm.

The Griseofulvin concentrations in water [mg/100 ml] were determined by means of a calibration curve given by $x = 0.6658y + 0.0017$; $r^2 = 0.9998$, Fig. 5, where x is the Griseofulvin concentration [mg/100 ml] and y is the absorption as measured. Each absorption measurement was repeated seven times.

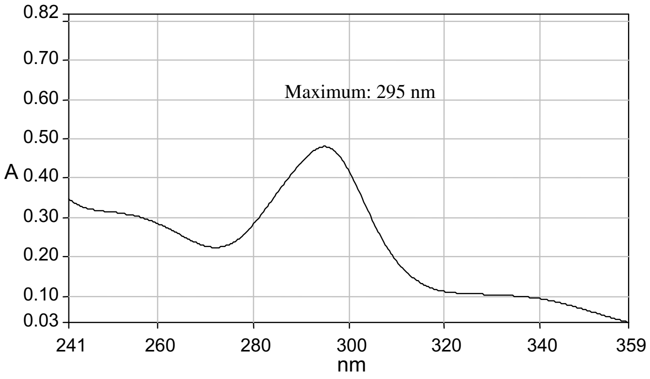

Fig. 4. UV/vis spectrum of Griseofulvin in water.

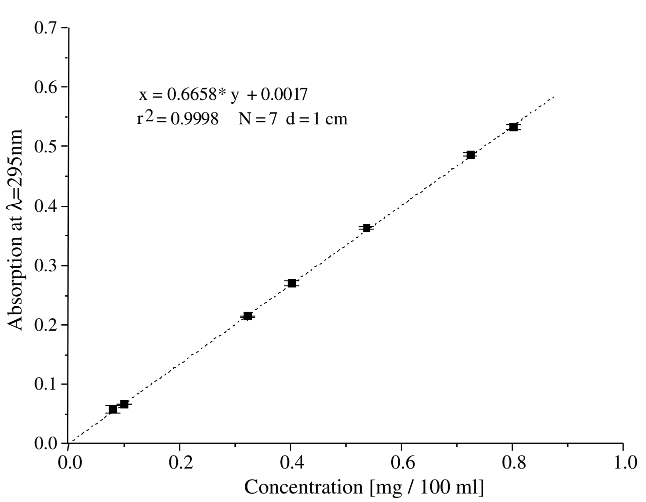

Fig. 5. Calibration curve used for the quantitative determination of Griseofulvin in water.

2.4. Dissolution enthalpy of Griseofulvin in water

2.4.1. Solubility of Griseofulvin at different temperatures

Due to its poor solubility in water and the slow rate of dissolution a calorimetric determination of the dissolution enthalpy of Griseofulvin at standard conditions (25 °C, $p = 1013$ hPa) was not possible. Therefore it was calculated from the temperature dependence of its solubility in water.

For this purpose an excess amount of Griseofulvin was suspended in distilled water and stored in tightly sealed vessels of brown glass at temperatures of 15, 25, 30, 40, 50 and 60 °C until a thermodynamic equilibrium of non-dissolved drug and supernatant was reached. For each temperature five samples were prepared. In order to find the time of reaching the dissolution equilibrium at 15 and 25 °C the Griseofulvin concentrations in the supernatant were determined after 0.5, 1, 1.5, 2, 3, 6, 9, 12, 24, 72 and 96 h. For the other temperatures the corresponding determinations were carried out after 24, 48, 72 and 96 h. By means of thin-layer chromatography it was shown that Griseofulvin was stable at the different storage temperatures over a storage period of more than 96 h. For the photometric determination of the Griseofulvin concentration in the supernatant the aqueous solution was filtered through a 0.22 μm filter which was washed before using another sample of the same solution. The filtered samples were diluted immediately to allow for a photometric determination of the drug concentration at $\lambda = 295$ nm. As the Griseofulvin concentration in the aqueous supernatant remained constant after 48 h, the concentration determined after a storage time of 72 h was considered as the equilibrium concentration K. It was used for the calculation of the dissolution enthalpies of Griseofulvin.

2.4.2. Calculation of the standard enthalpy, of the standard free energy and of the standard entropy of dissolution

According to van't Hoff [5] the temperature dependence of the solubility K of a compound at equilibrium is given by

$$\frac{d\ln K}{dT} = \frac{\Delta H^0_{sol}}{RT^2} \tag{2}$$

- ΔH^0_{sol} standard enthalpy of dissolution [J mol^{-1}].
- ΔS^0_{sol} standard entropy of dissolution [J mol^{-1} K^{-1}].
- R gas constant, 8.314 J mol^{-1} K^{-1}.
- T thermodynamic temperature [K]

By integration over the temperatures T_1 and T_2 Eq. (3) is obtained

$$\int_{T_1}^{T_2} d\ln K = \frac{\Delta H^0_{sol}}{R}\int_{T_1}^{T_2}\frac{dT}{T^2}$$

and

$$\ln\frac{K_1}{K_2} = -\frac{\Delta H^0_{sol}}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) \tag{3}$$

The standard enthalpy of dissolution can be calculated from the slope of a plot of $\ln K$ against $1/T$.

The standard free energy of dissolution ΔG^0_{sol} can be calculated by applying Eq. (4) [5]. As above K stands for the solubility of Griseofulvin at standard temperature $T^0 = 298$ K

$$-\Delta G^0_{sol} = RT^0\ln K \tag{4}$$

The standard entropy of dissolution ΔS^0_{sol} is calculated according to the Eq. (5)

$$\Delta S^0_{sol} = \frac{\Delta H^0_{sol} - \Delta G^0_{sol}}{T^0} \tag{5}$$

2.5. Thermal analyses

2.5.1. Differential thermal analysis/thermogravimetry

The melting behavior of Griseofulvin was studied by differential thermal analysis (DTA) combined with thermogravimetry (TG) using a Setaram DTA/TG calorimeter TG 92 (Setaram, Caluire, France). The instrument was calibrated using Indium with a purity of 99.999% (Fluka, Buchs, Switzerland) as standard. Its melting enthalpy is given by 3.283 ± 0.004 kJ mol^{-1}, melting point 156.6 °C [6]. The melting enthalpy ΔH_f^{MP} at the melting temperature as well as the melting temperature T_{MP} can be obtained directly by means of the Setaram software for each run.

2.5.2. High precision calorimetry

For direct determinations of the enthalpy of solution of Griseofulvin in water as well as of sublimation enthalpies of Griseofulvin we used a Setaram calorimeter C80 (Setaram, Caluire, France) which is constructed according to the Tian – Calvet principle [6]. The sensitivity of this equipment is in the range of 2–5 μW.

2.5.3. Determination of the enthalpy of melting by means of the C80 calorimeter

In order to achieve high precision results 250 mg of the substance to be studied was weighed (Balance: AT 21 Komparator, Mettler-Toledo GmbH, Giessen, Germany) into the calorimeter cell. Due to this relatively large amount of substance delays in the heat transition may occur. To correct this experimental error a temperature correction as suggested by Setaram was performed [8].

2.5.4. Direct determination of the enthalpies of solution

The direct determinations of the enthalpies of dissolution were performed according to the procedure described by Setaram [8]. Fig. 6 shows the geometry of the Setaram reversal mixing dissolution cell.

Fifty milligrams of the substance to be dissolved was weighed (Balance: AT 21 Komparator, Mettler-Toledo GmbH, Giessen, Germany) into the inner cylinder of the reversal mixing dissolution cell made from stainless steel. By means of mercury and a metallic disk the substance is sealed and separated from the solvent compartment. 5.0 g distilled water was added before the outer cylinder is tightly closed. The reference cell was prepared in the same way without the solute. Thereafter the two cells were put into the calorimeter C80 at 25 °C.

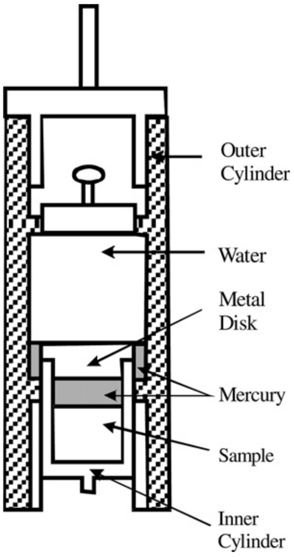

Fig. 6. Geometry of the Setaram dissolution cell (reversal mixing).

After thermal equilibration (1.5–2 h) the calorimeter C80 was continuously rotated by 180° forth and back. By this way the solute came into contact with the solvent. Mercury and the metal disk provided for stirring the mixture. The shaking was stopped when the signal reached the baseline again. The Griseofulvin solution was withdrawn from the sample cell to determine the amount of dissolved Griseofulvin by the method described above.

In order to validate the calorimetric setup the dissolution enthalpy of potassium chloride as reference was determined. Its dissolution enthalpy in water is given by $\Delta H_{sol} = 17.223$ kJ mol^{-1} [9].

2.5.5. Determination of the sublimation enthalpy

For the determination of the sublimation enthalpy of Griseofulvin stainless steel vacuum cells of Setaram, $V = 15$ cm^3, were used. By means of thin tubes of stainless steel the sample as well as the empty reference cell were connected to a vacuum pump (Vakubrand GmbH, Wertheim, Germany). In order to prevent that sublimated drug reaches the vacuum pump the tube coming from the sample cell passed a liquid nitrogen cooled trap, Fig. 7.

In the first step the sample was heated up to the desired temperature. When the baseline remained constant the valves between cells and vacuum pump ($p < 0.001$ bar) were opened to start the determination of the sublimation enthalpy. To control the full sublimation the sample cell was weighed before and after the sublimation. Immediately after the sublimation the stainless tube was taken out of the cold trap and rinsed with trichloromethane. The solution was used to check for stability of the sublimated drug by means of thin-layer chromatography. Degradation of Griseofulvin was not observed.

The setup for the determination was validated by means of hydroxybenzoic acid [10] and campher [9]. Excellent

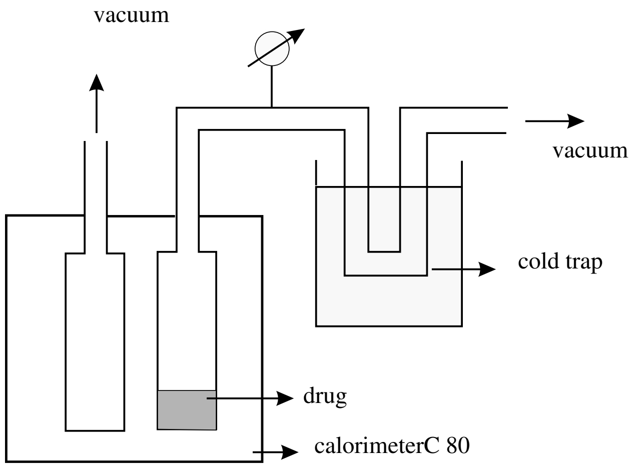

Fig. 7. Setaram vacuum cell for the determination of sublimation enthalpies.

agreement with the data reported in the literature was observed.

2.5.6. Calculation of the standard enthalpy and standard entropy of melting

The standard enthalpy of melting was calculated by means of the Kirchhoff equation describing the temperature dependence of the reaction enthalpy at constant pressure [5]

$$\Delta H_{\mathrm{f}}^{0} = \Delta H_{\mathrm{f}}^{\mathrm{MP}} - \int_{T^0}^{T_{\mathrm{MP}}} \Delta c_{\mathrm{p}}\, \mathrm{dT} \tag{6}$$

- $\Delta H_{\mathrm{f}}^{0}$ [J mol^{-1}] is the standard melting enthalpy at the standard temperature $T^0 = 298$ [K].
- $\Delta H_{\mathrm{f}}^{\mathrm{MP}}$ [J mol^{-1}] is the melting enthalpy at the melting point T_{MP}.
- Δc_{p} [J mol^{-1} K^{-1}] is the difference in heat capacities of the liquid and the solid phase.

The temperature dependence of the difference in the heat capacities Δc_{p} at constant pressure can be approximated by a polynomial $\Delta c_{\mathrm{p}} = a + bT$ [7].

$$\Delta H_{\mathrm{f}}^{0} = \Delta H_{\mathrm{f}}^{\mathrm{MP}} - \left[a \cdot \left(T_{\mathrm{MP}} - T^0\right) + \frac{1}{2} \cdot b \cdot \left(T_{\mathrm{MP}}^2 - \left(T^0\right)^2\right) \right] \tag{7}$$

The melting entropy $\Delta S_{\mathrm{f}}^{0}$ at T^0 is defined by [5]

$$\Delta S_{\mathrm{f}}^{0} = \Delta S_{\mathrm{f}}^{\mathrm{MP}} - \int_{T^0}^{T_{\mathrm{MP}}} \frac{\Delta c_{\mathrm{p}}}{T}\, \mathrm{d}T \tag{8}$$

which again is approximated by

$$\Delta S_{\mathrm{f}}^{0} = \Delta S_{\mathrm{f}}^{\mathrm{MP}} - \left[a \cdot \ln \frac{T_{\mathrm{MP}}}{T^0} + b \cdot \left(T_{\mathrm{MP}} - T^0\right) \right] \tag{9}$$

2.5.7. Calculation of the standard sublimation enthalpy

The standard sublimation enthalpy was calculated in analogy to the standardization of other enthalpies described above, see Eq. (6).

$$\Delta H_{\mathrm{sub}}^{0} = \Delta H_{\mathrm{sub}}^{T} - \int_{T^0}^{T} \Delta c_{\mathrm{p}}\, \mathrm{d}T \tag{10}$$

$T =$ sublimation temperature [K]

2.6. Thin-layer chromatography (TLC) of Griseofulvin

For stability tests of Griseofulvin the TLC method described in the East German pharmacopoeia 2AB [11] was used. Griseofulvin was dissolved in trichloromethane p.a. (Merck, Darmstadt, Germany). Ten microliters of the sample solution was placed on silica (Kieselgel G; Merck, Darmstadt, Germany). A mixture of methyl ethyl ketone/xylene, ratio 1:1, was used as mobile phase. The fluorescence of the samples was compared with the fluorescence of untreated Griseofulvin ($R_{\mathrm{f}} = 0.45$–0.55).

2.7. Quantum chemical calculation of the solvation energy of Griseofulvin

The solvation energy of Griseofulvin in water was calculated by means of AMSOL 6.1 (Quantum Chemistry Program Exchange, Program 606, Creative Arts Building, Indiana University, Bloomington, IN). Molecules can exist in several conformations. The statistical weight of a given conformer found by semiempirical methods was determined by means of the Boltzmann factor given in Eq. (11).

$$F_{\mathrm{B,i}} = \frac{\exp\left(\frac{-\Delta H_{\mathrm{f,i}}^{0}(\mathrm{gas})}{R \cdot T}\right)}{\sum_{\mathrm{j}} \exp\left(\frac{-\Delta H_{\mathrm{f,i}}^{0}(\mathrm{gas})}{R \cdot T}\right)} \tag{11}$$

- $F_{\mathrm{B,i}}$ is the Boltzmann factor
- $\Delta H_{\mathrm{f,i}}^{0}(\mathrm{gas})$ is the formation energy [kcal mol^{-1}] of a conformer in the gas phase at 298 K

The Boltzmann factors of the various conformers were calculated by means of the computer program SYBYL (SYBYL 6.2: Tripos Associates, 1699 St. Hanley Road, St. Louis, MO).

For conformers with large Boltzmann factors the free solvation energy in water was calculated according to equation

$$\Delta G_{\mathrm{solv,all}}^{0} = -R \cdot T \cdot \ln \left\{ \sum_{\mathrm{i}} \left[\frac{\exp\left(-\frac{\Delta H_{\mathrm{f,i}}^{0}(\mathrm{aq})}{R \cdot T}\right)}{\sum_{\mathrm{j}} \exp\left(-\frac{\Delta H_{\mathrm{f,j}}^{0}(\mathrm{aq})}{R \cdot T}\right)} \right] \cdot \exp\left(-\frac{\Delta G_{\mathrm{solv,i}}^{0}}{R \cdot \mathrm{T}}\right) \right\} \tag{12}$$

- $\Delta G_{\mathrm{solv,all}}^{0}$ total solvation energy [kcal mol^{-1}] at 298 K.
- $\Delta G_{\mathrm{solv,i}}^{0}$ solvation energy [kcal mol^{-1}] of a given conformer at 298 K.
- $\Delta G_{\mathrm{f,i}}^{0}(\mathrm{aq})$ energy of formation [kcal mol^{-1}] of a conformer in solution at 298 K.

3. Results

3.1. Enthalpy of dissolution

Due to the slow dissolution of Griseofulvin its dissolution enthalpy could not be determined by means of a calorimeter. Therefore it was determined from the solubility in dependence of the temperature, Table 1.

According to Eq. (3) the standard dissolution enthalpy of Griseofulvin can be calculated from the slope $-\Delta H_{\mathrm{sol}}^{0}/R$ of a plot of $\ln c_{\mathrm{s}}$ against $1/T$, Fig. 8. Its value is given by $\Delta H_{\mathrm{sol}}^{0} = -32.27$ kJ mol^{-1}.

Table 1
Solubility of Griseofulvin in water at different temperatures

Temperature [°C]	Solubility [mg/100 ml]	Solubility × 10^{-5} [mol/l]
15	0.63 ± 0.02	1.78 ± 0.05
25	1.03 ± 0.06	2.9 ± 0.2
30	1.18 ± 0.04	3.3 ± 0.1
40	1.71 ± 0.03	4.86 ± 0.09
50	2.59 ± 0.04	7.3 ± 0.1
60	4.1 ± 0.1	11.5 ± 0.4

The various standard energies of dissolution are summarized in Table 2.

3.2. Melting temperature and melt enthalpy

The melt enthalpy and the melting temperature of Griseofulvin were determined in a nitrogen atmosphere at a heating rate of 2 K/min. Both parameters proved to be independent from the sample mass. A melt enthalpy $\Delta H_f^{MP} = 34.1 \pm 0.3$ kJ mol^{-1} was measured for Griseofulvin. The melting temperature defined by T_{onset} is given by 219.14 ± 0.06 °C. At temperatures above the melting temperature due to degradation a slight mass decrease, 2.1 ± 0.2%, is observed.

In order to determine the standard melt enthalpy the difference Δc_p in the heat capacities of the solid as well as of the molten species has to be available. The corresponding data are shown in Fig. 9.

Considering the experimental error the temperature dependence of the heat capacity in the solid state can be approximated by

$$c_{p,solid} = -61.749 + 1.489 \cdot T\,[K]; \quad r^2 = 0.975$$

The temperature dependence of the heat capacity in the liquid state is given by

$$c_{p,liquid} = -362.377 + 2.495 \cdot T\,[K]; \quad r^2 = 0.950$$

The difference in the heat capacities is given by

$$\Delta c_p = c_{p,liquid} - c_{p,solid} = -300.628 + 1.006 \cdot T\,[K]$$

With $a = -300.628$ and $b = 1.006$ the standard melt enthalpy can be calculated using Eq. (9). With $\Delta H_f^{MP} = 34.1$ kJ mol^{-1}, $T_{MP} = 492.29$ [K] and $T^0 = 293.15$ [K] the standard melt enthalpy is given by $\Delta H_f^0 = 15.3$ kJ mol^{-1}.

3.3. Sublimation enthalpy

The sublimation enthalpy for Griseofulvin was determined at three temperatures, see Table 3. As proven by TLC the substance remained stable during the whole process.

For the sublimation entropy ΔS_{sub} at 205 °C a value of 320.9 J mol^{-1} K^{-1} is calculated. The Gibbs free energy of sublimation ΔG_{sub} is given by 57.8 kJ mol^{-1}.

The difference between the heat capacities of the solid and the vapor phase could not be determined. Therefore

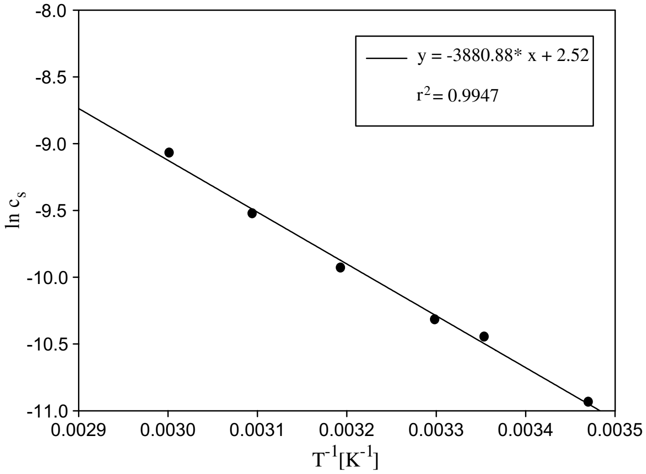

Fig. 8. Plot for the determination of the dissolution enthalpy of Griseofulvin in water.

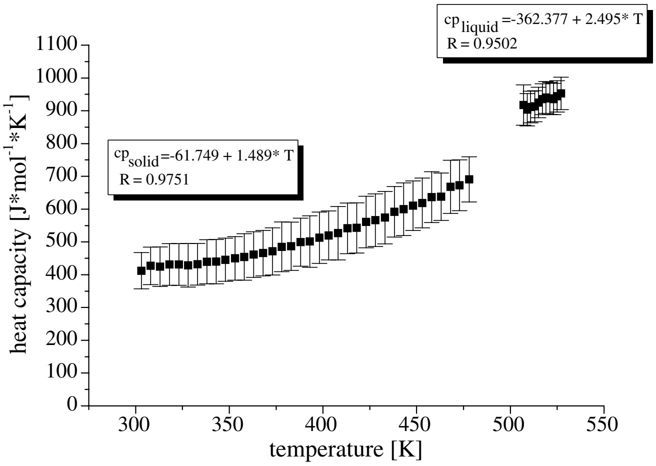

Fig. 9. Heat capacities of Griseofulvin in the solid as well as in the liquid state.

Table 2
Griseofulvin – standard energies of dissolution

		Equation to be used
Standard Gibbs free energy ΔG^0_{sol}	−25.9 kJ mol^{-1}	4
Standard enthalpy ΔH^0_{sol}	−32.27 kJ mol^{-1}	3
Standard entropy ΔS^0_{sol}	21.1 J mol^{-1} K^{-1}	5

Table 3
Sublimation enthalpy ΔH_{sub} of Griseofulvin

Temperature [°C]	Sublimation enthalpy ΔH_{sub} [kJ mol^{-1}]
200	152.9 ± 2.9
205	155.2 ± 2.4
210	151.9 ± 1.9
Average	153.4 ± 1.4

Table 4
Quantum chemical calculations for the most important conformers of Griseofulvin

Nr.	ΔH^0(gas) [kcal mol^{-1}]	Boltzmann-Factor	ΔH^0(aq) [kcal mol^{-1}]	ΔG^0(Pol) [kcal mol^{-1}]	ΔG^0(CDS) [kcal mol^{-1}]	ΔG^0(solv) [kcal mol^{-1}]
1	−162.129	0.00200	−159.408	−11.882	0.05	−9.11
2	−162.963	0.00818	−160.254	−11.939	−0.085	−9.315
3	−162.222	0.00234	−159.62	−11.548	0.074	−8.874
5	−162.774	0.00595	−160.073	−11.793	−0.046	−9.138
6	−162.552	0.00409	−159.84	−12.011	−0.116	−9.416
11	−162.639	0.00473	−159.93	−11.853	−0.053	−9.197
12	−163.761	0.03151	−160.131	−14.839	0.672	−10.537
13	−163.842	0.03613	−160.33	−14.557	0.672	−10.373
15	−164.358	0.08641	−160.83	−14.43	0.756	−10.146
16	−162.265	0.00252	−159.271	−12.673	−0.124	−9.802
18	−162.992	0.00859	−160.304	−11.709	0.062	−8.959
22	−161.847	0.00124	−158.879	−12.475	0.039	−9.468
23	−162.157	0.00210	−159.49	−11.645	0.084	−8.894
25	−163.105	0.01040	−160.479	−11.585	0.066	−8.892
27	−161.412	0.00060	−158.755	−11.92	−0.073	−9.936
28	−163.55	0.02206	−160.039	−14.359	0.789	−10.059
30	−162.121	0.00197	−159.476	−11.657	0.082	−8.93
33	−164.614	0.13317	−161.502	−13.137	0.637	−9.328
34	−163.47	0.01927	−159.849	−14.595	0.785	−10.189
35	−162.241	0.00242	−159.634	−11.53	0.071	−8.851
39	−165.031	0.26941	−161.895	−12.974	0.755	−9.083
47	−162.675	0.00503	−159.715	−12.549	−0.082	−9.672
52	−161.145	0.00038	−158.176	−12.6	−0.086	−9.718
54	−164.365	0.08744	−161.043	−13.672	0.566	−9.784
55	−164.271	0.07459	−160.646	−14.669	0.757	−10.286
56	−164.784	0.17748	−161.479	−13.59	0.603	−9.681

the calculation of standard energies of sublimation was impossible.

3.4. *Quantum chemical calculation of the solvation enthalpies of Griseofulvin*

As a first step in the quantum chemical calculation of solvation energies of Griseofulvin in water a conformation analysis was performed. For each relevant conformer the formation energy in the gas phase, ΔH_f^0(gas), and the Boltzmann factor were calculated. The results are summarized in Table 5. In addition for each conformer the formation enthalpy in water ΔH^0(aq), the free energy of polarization ΔG^0(Pol), the cavitation-dispersion-solvent-structural free energy ΔG^0(CDS) and the free energy of solvation ΔG^0(solv) are included.

By means of the data of Table 4 and Eq. (12) the solvation energy $\Delta G^0_{\text{solv}} = \Delta G^0_{\text{solv,all}}$ was calculated. Its value is given by $\Delta G^0_{\text{solv}} = -40.2\ \text{kJ mol}^{-1}$.

3.5. *Discussion of the dissolution process of Griseofulvin*

The thermodynamic data gathered so far experimentally as well as by quantum chemical calculations allow for an analysis of the dissolution process of Griseofulvin in the framework of the Hess theorem.

Table 5
Standard entropies ΔS^0 of Griseofulvin obtained for the three steps of process 1

Standard entropy ΔS^0_{subl}	293.0 J mol^{-1} K^{-1}
Standard entropy ΔS^0_{solv}	−271.5 J mol^{-1} K^{-1}
Standard entropy ΔS^0_{sol}	−21.5 J mol^{-1} K^{-1}

As can be seen from Fig. 2 the dissolution of a solid to form a solution can be split up into three alternative processes. As the starting and endpoints of all these processes are always the same the corresponding state functions must sum up to zero.

Process 1: solid → sublimation (gaseous state) → transfer of the sublimated molecules into cavities formed in the solvent → solvation of the molecules in the solvent → solution

Process 2: solid → melting → evaporation of the melt (gaseous state) → transfer of the sublimated molecules into cavities formed in the solvent → solvation of the molecules in the solvent → solution

Process 3: solid → melting → mixing with solvent at a pressure that allows for having the temperature of the melting point of the solid → expansion and cooling down to standard conditions → solution

These processes always consist of an endothermic (sublimation or melting and evaporation) and an exothermic step (solvation or mixing). The sum of the free energies ΔG of the two steps determines the driving force of the dissolution process and hence the solubility of the solid in the given solvent.

Whereas process 3 is more of theoretical importance the processes one and two allow to better understand the dissolution of a solid in a given solvent. Process 1 shall be discussed in more detail.

3.5.1. *Thermodynamical parameters of process 1*

For process 1 the following sums of state functions can be defined:

$$\Delta G^0_{\text{subl}} + \Delta G^0_{\text{solv}} + \Delta G^0_{\text{sol}} = 0 \tag{13}$$

$$\Delta H^0_{\text{subl}} + \Delta H^0_{\text{solv}} + \Delta H^0_{\text{sol}} = 0 \tag{14}$$

$$\Delta S^0_{\text{subl}} + \Delta S^0_{\text{solv}} + \Delta S^0_{\text{sol}} = 0 \tag{15}$$

Using the data determined experimentally or by quantum chemical calculations one obtains from Eq. (13):

$$\Delta G^0_{\text{subl}} = -\Delta G^0_{\text{solv}} - \Delta G^0_{\text{sol}} = 40.2 + 25.9 = 66.1\ \text{kJ mol}^{-1}$$

Experimentally a free energy of sublimation ΔG_{subl} of 57.8 kJ mol^{-1} was determined. The difference $\Delta G^0_{\text{subl}} - \Delta G_{\text{subl}} = 8.3$ kJ mol^{-1} is primarily due to the fact that the experimentally determined Gibbs free energy of sublimation ΔG_{subl} could not be standardized as c_p(gas) is not available.

The standard solvation enthalpy ΔH^0_{solv} can be calculated from Eq. (14). Under the assumption that the enthalpy of sublimation is temperature independent the experimentally determined value of $\Delta H_{\text{subl}} \approx \Delta H^0_{\text{subl}} = 153.4$ kJ mol^{-1}, Table 3, can be used for the calculation. The standard solvation enthalpy of Griseofulvin is then given by

$$\Delta H^0_{\text{solv}} = -\Delta H^0_{\text{subl}} - \Delta H^0_{\text{sol}} = -153.4 + 32.3$$
$$= -121.1\ \text{kJ mol}^{-1}$$

By means of the standard Gibbs free energies ΔG^0 and the standard enthalpies ΔH^0 of the three steps of process 1 the corresponding standard entropies ΔS^0 can be calculated. They are summarized in Table 6.

By means of the standard entropies ΔS^0 the entropic contributions, $-T \times \Delta S^0$, to the standard Gibbs free energies ΔG^0 can be calculated for the three steps of process 1. Together with the enthalpic contributions ΔH^0 to the standard Gibbs free energies they are summarized in Table 7.

A look at these data shows that the entropic contribution of the solvation step almost can compensate for the entropic contribution of the sublimation step. However this does not hold for the corresponding enthalpic contributions. The energy required to separate the Griseofulvin molecules from each other is much higher than the energy released in the solvation step. This difference limits the solubility of Griseofulvin.

Table 6
Enthalpic and entropic contributions to the Gibbs free energies for the three steps of process 1, $T = 298$ [K]

Step	Enthalpic contribution ΔH^0 [kJ mol^{-1}]	Entropic contribution $-T\,\Delta S^0$ [kJ mol^{-1}]
Sublimation	153.4	−87.3
Dissolution	−32.3	6.4
Solvation	−121.1	80.9

Table 7
Comparison of mixing energies of Griseofulvin and water as determined experimentally and calculated under the assumption of idealistic behavior

	Real solution	Ideal solution	Difference
ΔH^0_{mix} [J mol^{-1}]	16,822	0	16,822
ΔG^0_{mix} [J mol^{-1}]	17,967	− 20.2	17987.2
ΔS^0_{mix} [J mol^{-1} K^{-1}]	−3.84	−0.067	−3.91

3.5.2. *Thermodynamical parameters of process 2*

By means of the experimental data obtained for Griseofulvin the energies of further steps from Fig. 2 can be calculated. The standard evaporation enthalpy ΔH^0_{evap} is given by

$$\Delta H^0_{\text{evap}} = \Delta H^0_{\text{sub}} - \Delta H^0_{\text{f}} = 153.4 - 15.3 = 138.1\ \text{kJ mol}^{-1}$$

As mentioned above ΔG^0_{f} could not be determined. In consequence ΔG^0_{evap} and ΔS^0_{evap} cannot be calculated.

The solvation energies are the same as in process 1.

3.5.3. *Thermodynamical parameters of process 3*

The standard enthalpy of mixing can be obtained by

$$\Delta H^0_{\text{mix}} = \Delta H^0_{\text{sol}} - \Delta H^0_{\text{f}} = 32.2 - 15.3 = 16.9\ \text{kJ mol}^{-1}.$$

As performed under standard conditions this equation encomprises the expansion of the solvent to standard pressure as well as its cooling down to standard temperature.

For an ideal solution the Gibbs free mixing energy is given by [12]

$$\Delta G^0_{\text{M}} = -RT \cdot (X_a \ln X_a + X_b \ln X_b) \tag{16}$$

The standard entropy of mixing in analogy is given by [12]

$$\Delta S^0_{\text{M}} = -R \cdot (X_a \ln X_a + X_b \ln X_b) \tag{17}$$

X_a, X_b ideal solubilities of the components expressed as mole fractions. The corresponding value for Griseofulvin is given by $X_a = 5.276 \times 10^{-7}$ and $X_a + X_b = 1$. A comparison of the experimentally determined mixing energies with the corresponding values calculated under the assumption of having an ideal solution is given in Table 7.

In Table 7 the differences between the energies of real and ideal solutions, the so-called excess functions, are given. They describe the extent of deviation from the ideal solution. Great endothermic values indicate strong interactions between the molecules of the solute. Negative mixing entropies show that the solvent and solute molecules do not mix spontaneously. This interpretation is supported by a high value of the free energy of mixing. This means that strong solvent–solvent interactions as well as solute–solute interactions cannot be compensated by the formation of new solvent–solute interactions. These findings support the interpretation of the thermodynamical parameters of process 1.

4. Conclusions

Due to its small amount the determination of the dissolution energy of Griseofulvin is very difficult. In addition it gives only little insight into the dissolution process. Therefore a series of alternative processes was conceived according to the Hess theorem. This allowed to determine the energies associated with sublimation as well as with melting and with evaporation of the test substance whereas the transfer energy as well as the solvation energy were calculated quantum chemically. An evaluation of these data showed that the large sublimation energies on one hand and the relative low solvation energies are the key factors limiting the solubility of Griseofulvin. Based on these findings one could expect a significant improvement of the solubility of Griseofulvin in water if during the manufacture of the dosage form the Griseofulvin molecules could be fixed in the energy-rich state of sublimation. This could be achieved by fixing the molecularly dispersed drug molecules in a hydrophilic carrier in a glassy state i.e. by the formation of so-called solid solution. Unfortunately so far Griseofulvin was embedded e.g. in PEG or other rubbery polymers [13] which are unable to fix the molecularly dispersed molecules and therefore allow for re-crystallization.

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